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Therapy and Prevention of Thrombotic Thrombocytopenic Purpura During Pregnancy: A Clinical Study of 16 Pregnancies

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Thrombotic thrombocytopenic purpura (TTP) is a severe multisystem disorder of unknown pathogenesis, with preference to women. The mortality rate of patients with TTP was 90% until the introduction of plasma therapy that increased the survival rate to 70–80%, with minimal or no sequelae. Of the survivors, 30–60% suffer from relapses, often in association with precipitating factors such as infections, surgery, and pregnancy. Women who are either pregnant or in the postpartum period make up 10–25% of TTP patients, and once the disease occurs during a pregnancy, it tends to recur in subsequent ones. We treated five women who suffered at least one TTP episode during pregnancy. They had a total of 16 pregnancies, eight of which were complicated by TTP. They suffered seven additional TTP episodes that were not associated with pregnancy. We assessed the severity of each TTP episode with a scoring system used in our previous studies. Presented is the course of their disease and their pregnancies, and guidelines for the management and prevention of TTP during pregnancy are provided. © 1996 Wiley-Liss, Inc.

Key words: aspirin; dipyridamole, pregnancy, plasmapheresis, relapsing thrombotic thrombocytopenic purpura, TTP

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a severe multisystem disorder of unknown pathogenesis, characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurologic symptoms and signs, and impaired renal function [1,2]. The median age at diagnosis is 35 years, and the female to male ratio is 3:2 [1,2]. In the past, the mortality rate of patients with TTP was 90% [2], but since the introduction of plasma therapy, 70–80% of patients survive with minimal or no sequela [1–7]. Unfortunately, 30–60% of these survivors suffer from relapses, often in association with precipitating factors such as infections, surgery, and pregnancy [3,5].

Women who are either pregnant or in the postpartum period make up 10–25% of TTP patients [1,2]. Case reports indicate that once the disease occurs during a pregnancy, it tends to recur in subsequent ones [8–10]. Data on the management of TTP during pregnancy are scant, are based on case reports [8–16], and do not deal with the issue of prevention of relapses.

Between the years 1985 and 1992, the authors treated 17 patients with TTP, five of whom suffered at least one episode during pregnancy. The five women had a total of 16 pregnancies during this period, eight of which were complicated by TTP. The five suffered seven additional TTP episodes that were not associated with pregnancy. We describe the course of their disease and their pregnancies and provide guide lines for the management and prevention of TTP during pregnancy.

METHODS

Patients

Medical charts and the plasmapheresis unit records of the five patients were reviewed. Criteria necessary for

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TABLE I. Severity Score of Relapsing TTP*

Score	Neurologic signs	Renal function disorder	Platelet count at presentation ($\times 10^6$/L)	Hgb at presentation (g/dL)
0	None	None	>100	>12
1	Confusion, lethargy, behavioral changes	30mg/dL<BUN<70mg/dL and/or 1.5mg/dL<creatinine<2.5mg/dL and/or proteinuria>2g/day and/or hematuria	20–100	9–12
2	Focal neurologic deficits, convulsions, stupor, coma	BUN>70 mg/dL and/or creatinine>2.5 mg/dL and/or dialysis	<20	<9

*BUN, blood urea nitrogen; Hgb, hemoglobin.

the diagnosis of TTP included thrombocytopenia, MAHA, and neurological symptoms and/or signs. Thrombocytopenia and MAHA were regarded as sufficient for the diagnosis of a relapse [3]. Remission was defined when a platelet count above $10^6/\mu L$ was maintained for 4 weeks. The pregnancy and postpartum period was defined from conception to 6 weeks after delivery.

We assessed the severity of each TTP episode with a scoring system used in our previous studies (Table I) [1,3–5]. The patients' severity scores (SS) ranged from a minimum of 0 (no evidence of disease) to a maximum of 8 (severe TTP).

Statistical Analysis

The two-sample t-test and the non-parametric Mann-Whitney test were used to make three comparisons of severity scores: i) between TTP episodes associated with pregnancy and not associated with pregnancy; ii) between patients who received and did not receive prophylactic therapy; and iii) between cases in which the fetuses survived and those in which they died. The paired t-test and the Wilcoxon rank-sum test were applied for the assessment of change in severity score between different TTP episodes in the same woman. The Fisher's exact test for contingency tables was used for comparing pregnancy outcome between women treated and not treated with prophylactic therapy.

CASE REPORTS

Patient 1

This patient developed severe thrombocytopenia, MAHA, stupor, and fever at the age of 19 during the 20th week of her first pregnancy, and was diagnosed as suffering from TTP (SS 8). Her second episode occurred 2 years later during the 20th week of her second pregnancy (SS 8). Both pregnancies were terminated because of fetal death, and in both cases the patient required intensive therapy, including frequent plasma exchanges and peritoneal dialysis. Five years later, during the 8th week of her third pregnancy, an elective abortion was performed in order to prevent a TTP relapse, and the patient developed no evidence of disease. When she conceived again a year later, she refused to terminate the pregnancy. Prophylactic therapy with aspirin (100 mg/day) and dipyridamole (225 mg/day) was prescribed and the patient was well until the 38th week when she developed mild thrombocytopenia (SS 1). She was treated with plasma exchange, delivered a healthy baby at term, and the TTP relapse resolved 2 weeks postpartum. The patient remained well for 6 years and conceived again at the age of 31. She was treated again with aspirin and dipyridamole, but the pregnancy was terminated in the 20th week because of fetal death. She received fresh frozen plasma (FFP) and hydrocortisone as prophylaxis and developed no signs of TTP. During the last 2 years, she has not conceived and has had no additional TTP relapses. Partial data from this patient have been published previously. [8,11].

Patient 2

This patient's first TTP episode (SS 6) occurred at the age of 30 and was not associated with pregnancy. She had her second episode 4 years later during the 25th week of her first pregnancy (SS 4), and responded to FFP and plasma exchange. The pregnancy was terminated because of fetal death. The woman then completed two pregnancies to term with no evidence of TTP while receiving prophylactic therapy with aspirin (100 mg/day) and dipyridamole (225 mg/day). During her fourth pregnancy the patient complied only partially with the same prophylactic

therapy, and in the 35th week she developed a relapse (SS 2) complicated by preeclampsia. She was treated with FFP and plasma exchanges and delivered a healthy baby at 37 weeks. TTP resolved 3 weeks postpartum after intensive therapy. She has subsequently completed three additional pregnancies, despite complying only partially with prophylactic treatment of aspirin and dipyridamole and has had no additional episodes of TTP. Partial data from this patient have been published previously [8].

Patient 3

This patient suffered her first TTP episode (SS 5) at the age of 28 during the 17th week of her first pregnancy, which resulted in fetal death. The woman did not enter remission despite treatment with over 1,000 units of plasma, and the disease episode ended only after she underwent splenectomy. Three months later, she suffered a relapse (SS 4) which was successfully treated with plasma exchange, corticosteroids, aspirin, and dipyridamole, and has remained well since.

Patient 4

This patient suffered her first episode of TTP (SS 7) at the age of 22, 1 month after her second delivery, with severe thrombocytopenia, MAHA, and renal and neurological disease. She was thought to have systemic lupus erythematosus and was treated with cyclophosphamide, corticosteroids, assisted ventilation and peritoneal dialysis with a slow response. The diagnosis of TTP was made only 9 months later when she developed a severe relapse (SS 7), and responded to plasma therapy and peritoneal dialysis. Three months later she developed her third episode of severe TTP (SS 8) and succumbed 12 hours after presentation with multi-organ failure.

Patient 5

This patient's first two episodes of TTP occurred when she was 19 and 20 years old (SS 5 and 2, respectively), and neither episode was associated with pregnancy. She presented at the age of 21 in the 9th week of her first pregnancy with mild TTP (SS 2) and follicular tonsillitis. She was treated for the acute episode and successfully completed her pregnancy to term while on prophylactic therapy with aspirin, dipyridamole, and prednisone. She developed a relapse of TTP 3 months after delivery (SS 3) which responded promptly to therapy and subsequently underwent splenectomy in an effort to prevent further relapses. She has remained well since.

RESULTS

We have treated five women with relapsing TTP, each of whom suffered at least one episode during pregnancy (Tables II and III). The women had a total of 15 TTP episodes, eight of which were associated with pregnancy and/or the postpartum period. The average age at their first TTP episode was 23.6 with a range of 19–30. In four of the women (80%), TTP occurred during their first pregnancy although two patients (Patients 2 and 5) had already had one and two episodes of TTP, respectively, prior to pregnancy; the fifth woman (Patient 4) had an uneventful first pregnancy and suffered her first bout of the disease 4 weeks after her second delivery (Table III).

TTP occurred during the first trimester of one pregnancy, during the second trimester of four, and in two cases it appeared shortly before delivery and continued postpartum (Table III). In the eighth pregnancy, TTP appeared 1 month postpartum. The average week of pregnancy in which TTP appeared was 23, with a range of 9 to 38 weeks (Table III). Of the seven episodes in which TTP occurred during the actual pregnancy, three were completed to term and resulted in the normal delivery of a healthy baby; in the remaining four (57%), the fetus died and the pregnancy was terminated during the second trimester. There were no maternal deaths from TTP episodes associated with pregnancy, but one of the women (Patient 4) died during a relapse not associated with pregnancy.

Among the eight pregnancies not complicated by TTP, six ended in the normal, full-term delivery of healthy babies and one in intrauterine fetal death. The eighth pregnancy was terminated by an elective abortion.

There was no significant difference in severity score between TTP episodes occurring during pregnancy and those not associated with pregnancy (4.6 versus 5.0, respectively, $P = 0.78$). There was also no significant change in severity score between first and second, first and third, and second and third TTP episodes in the same woman. The average severity score in the episodes of TTP during pregnancy in which the fetuses survived, 1.67, was significantly lower than the average score in the episodes in which the fetuses died, 6.25 ($P = 0.014$).

Therapy

Twelve of the 15 episodes were treated with plasmapheresis, with the dose of plasma infused ranging from 20 to over 1,000 units (Patient 3). Plasmapheresis was not used in three cases. In the first, the diagnosis of TTP was not made (first episode of Patient 4), in another the patient succumbed within 12 hours of arrival at the hospital (third episode of Patient 4), and in the third, the episode was mild and the patient recovered after the infusion of 10 units of plasma (second episode of Patient 5). All patients received corticosteroids at an initial dose equivalent to 300 mg of hydrocortisone per day, with the dose being tapered gradually during remission. In addition, all patients received aspirin (100–500 mg/day) and dipyridamole (225 mg/day). In four of the episodes, vincristine

TABLE II. Summary of Patients, Pregnancies, TTP Episodes, and Overall Outcome

Patient no.	Age at first TTP episode	Total no. of pregnancies	Total no. of TTP episodes	No. of TTP episodes in pregnancy	Total no. of live births	Maternal outcome
1	19	5	3	3	1	Survived
2	30	7	3	2	6	Survived
3	28	1	2	1	0	Survived
4	22	2	3	1	2	Died during 2nd relapse
5	19	1	4	1	1	Survived
Total		16	15	8	10	

TABLE III. TTP Episodes

Patient no.	Age	TTP episode no.	Pregnancy no.	Gestational age (weeks)	Prophylaxis	Severity score	Outcome of pregnancy	Outcome of patient
1	19	1	1	20	No	8	IUFD	Survived
	21	2	2	20	No	8	IUFD	Survived
	28	3	4	38	Yes	1	ND	Survived
2	30	1	NP	—	No	6	—	Survived
	34	2	1	25	No	4	IUFD	Survived
	37	3	4	35	Yes	2	ND	Survived
3	28	1	1	17	No	5	IUFD	Survived
	28	2	NP	—	No	4	—	Survived
4	22	1	2	PP	No	7	ND	Survived
	22	2	NP	—	No	7	—	Survived
	23	3	NP	—	No	8	—	Died
5	19	1	NP	—	No	5	—	Survived
	20	2	NP	—	Yes	2	—	Survived
	21	3	1	9	Yes	2	ND	Survived
	22	4	NP	—	Yes	3	—	Survived

IUFD, intrauterine fetal death; ND, normal delivery; NP, not pregnant; PP, post partum.

was administered at an intravenous dose of 2 mg/week for 1–4 weeks. Patient 3 underwent splenectomy when remission was not achieved after 4 months of repeated plasma exchanges, corticosteroids, vincristine, and high dose gammaglobulin, and responded with marked increase of the platelet count.

Prophylactic Therapy

Five of the ten TTP relapses occurred while the patients were receiving prophylactic therapy with aspirin (100 mg/day) and dipyridamole (225 mg/day). Patient 5 suffered two relapses while on prednisone 20 mg/day in addition to these anti-platelet agents, and had to undergo splenectomy to prevent further relapses (after the splenectomy, the platelet count increased to over $6 \times 10^6/\mu L$ within a 3 week period, and the patient has been followed up for more than 3 years now). However, the mean severity score of the five TTP relapses that occurred while the patients were on prophylactic therapy (2.0) was significantly lower than the mean score of the five relapses that occurred without prophylaxis (6.2, $P = 0.025$). Prophylactic therapy also improved pregnancy outcome. Of the seven pregnancies complicated by TTP before delivery, the three in which the mothers received prophylactic therapy were completed successfully to term, while the four in which no prophylaxis was given ended in intrauterine fetal death. ($P = 0.028$, see Table III).

DISCUSSION

We describe five women with relapsing TTP who had a total of 16 pregnancies, eight of which were complicated by the disease. Fetal mortality was 50% in pregnancies associated with TTP, and one mother died in a relapse not associated with pregnancy. This study demonstrates that, as expected, pregnancy complicated by mild TTP (low SS) is more likely to result in a normal delivery than pregnancy complicated by severe TTP. Prophylactic therapy with aspirin and dipyridamole in women with a history of TTP significantly reduces the severity of relapses, as assessed by the severity score, and improved pregnancy outcome.

Weiner [15] reviewed the 45 cases of TTP in pregnancy published from 1966–1985 and found that the mean ma-

ternal age was 23, the disease developed in the antepartum period in 89% of cases, and the mean gestational age at onset was 23.5 weeks. these results were similar to ours. However, Weiner found a maternal mortality rate of 44% and a perinatal mortality rate of 80%, both higher than in our patients. These differences probably reflect the improvement in prognosis caused by the introduction of plasma therapy over the last 15 years [3,5–7]. In Weiner's study [15], there were no deaths among the 17 women who received plasma therapy.

In Weiner's review [15] only one woman had relapsing disease, and, until recently, relapsing TTP during pregnancy had only been described in a few case reports [8–10]. Our previous studies [3,5] have demonstrated that TTP has a relapse rate of 30–60%, with pregnancy being a major inciting factor. Other inciting factors include oral contraceptives, infections, surgery, invasive procedures, and peptic ulcer disease [3,5]. All five women in this study suffered from relapsing disease, with the disease recurring during subsequent pregnancies in two of the patients (patients 1 and 2).

TTP in pregnancy must be differentiated from two other conditions associated with microangiopathy, hemolytic uremic syndrome (HUS) and preeclampsia-eclampsia syndromes [13–15]. Pregnancy-related HUS usually occurs in the postpartum period and is characterized by severe acute renal failure, MAHA, and thrombocytopenia, but neurological manifestations are rare [13–15]. Preeclampsia-eclampsia patients may have fever, seizures, microangiopathic anemia, and thrombocytopenia, but the hematological manifestations are much milder than in TTP. A decline in antithrombin III has been described in preeclampsia-eclampsia and not in TTP, and may help to differentiate these disorders [15]. This distinction is essential, as the treatment of TTP does not always necessitate termination of the pregnancy. (see below).

The pathogenesis of TTP remains obscure, with the histological features of platelet thrombi occluding capillaries and arterioles pointing to a pathological interaction between endothelium and platelets [1,2]. Plasma from patients with chronic relapsing TTP contains usually large von Willebrand Factor (vWF) multimers, which disappear during relapses [17]. Patients with a single episode of TTP have either unusually large vWF multimers or a relative decrease in the largest plasma vWF forms, depending on the stage of their disease. These abnormalities disappear during remission [18]. Plasma from several TTP patients has also been found to contain a platelet clumping factor [19] and to have abnormalities in prostacyclin synthesis and stability [20]. Neonatal and fetal thrombocytopenia and anemia have not been reported in pregnancies complicated by TTP, indicating that the factor causing the disease does not cross the placenta [21]. The cause of fetal death in TTP is believed to be placental infarcts caused by the maternal disease [21].

Plasma exchange is the treatment of choice for an acute TTP episode, although it is still unclear whether the benefits of this therapy are due to removing an injurious factor, infusing a deficient factor or both [1]. Patient's plasma should be replaced by FFP or the cryosupernatant fraction of plasma [1]. Patients should also be treated with corticosteroids (prednisone 1 mg/kg or equivalent), aspirin (100 mg/day), and dipyridamole (225 mg/day), with vincristine reserved for severe cases [1,2]. TTP patients with high severity scores (above 4) should be treated with all modalities of therapy simultaneously, including plasmapheresis and plasma infusions, platelet inhibitor drugs, high dose corticosteroids and vincristine [1]. This intensive therapy should be continued two to three days after normalization of clinical and laboratory parameters and then tapered off gradually [1].

Splenectomy should be performed in patients who are dependent on plasma therapy to maintain remission or who have frequent, disabling relapses [1,3].

In pregnant women the therapeutic approach should be even more aggressive, and women with any evidence of disease should be treated immediately with all therapeutic modalities. Vincristine should not be given if the fetus is alive. The pregnancy should not be terminated if the fetus is alive, as this does not cure the disease, and with intensive therapy both the mother and fetus may survive [1,3,5,8–10]. In three of the pregnancies described in this study the disease continued or started postpartum despite the normal delivery of a healthy baby.

Women of childbearing age with a history of TTP should be advised of the high risk of recurrence during pregnancy, and if they do become pregnant, termination of pregnancy should be considered. If the woman wishes to continue the pregnancy, she should receive prophylactic therapy with aspirin 100 mg/day and dipyridamole 225 mg/day. The value of this regimen was clearly demonstrated in this study, women who relapsed on this regimen had significantly milder relapses, and pregnant women who received this therapy delivered healthy babies at term. Prophylaxis with additional therapeutic modalities such as corticosteroids and plasma may be considered when the risk of relapse is especially high (a severe infection during pregnancy, an abortion, or a past history of severe relapses during pregnancy). Although these recommendations are based on a retrospective study, prospective and controlled studies are very difficult to conduct in this rare disease. Further progress in TTP therapy and prevention awaits the elucidation of the disease's pathogenesis.

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